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Draft

Internationally Harmonised Guide for Active Pharmaceutical Ingredients

Good Manufacturing Practice

(API Guide)

September 1997

This guide was prepared by a multinational working group consisting of the following members:

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Note: Representatives from Indian and Japanese regulatory authorities were invited but unable to attend the meetings of the working group but were kept informed of the progress achieved.

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1 Introduction

1.1 Purpose

This document is intended to provide guidance regarding current good manufacturing practice (CGMP) for the manufacture, processing, packing, or holding (storage) of active pharmaceutical ingredients (APIs) to ensure that the APIs are manufactured under a quality management system and that all APIs meet requirements for purity, identity, safety and quality which they purport or are represented to possess. This document does not affect the ability of the responsible regulatory agency to establish specific requirements or standards regarding APIs within the context of new drug application reviews. Likewise, this document is not intended to address specific issues relating to filings of such applications.

Although this document focuses on the manufacture of APIs, it may also be useful as a guide for the manufacture of excipients.

The Guide as a whole does not cover safety aspects for the personnel engaged in the manufacture, nor aspects of protection of the environment: their control are inherent responsibilities of the manufacturer and are governed by national legislations.

In this Guide the term "should" indicates requirements that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance.

1.2 Scope

This document applies to the manufacture of APIs for use in human and veterinary drug products.

It applies to the manufacture of APIs used in the production of drug (medicinal) products for clinical trials.

It applies to the manufacture of sterile APIs only up to the point immediately prior to the API being rendered sterile. Sterilisation and aseptic processes should be carried out according to the CGMP requirements applicable to sterile finished dosage forms.

It applies to the later chemical isolation and purification steps of an API derived from the biological, biotech or fermentation process.

It does not apply to medicinal gases, final dosage forms and manufacturing or control aspects specific to radiopharmaceuticals.

1.3 Definitions

Active Pharmaceutical Ingredient (API)

Any substance that is represented for use in a drug (medicinal product) in the manufacturing, processing or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body of man or other animals. APIs include substances manufactured by processes such as: chemical synthesis, fermentation, recombinant DNA or other biotechnology methods, isolation/recovery from natural sources, or any combination of these processes.

Batch (or Lot)
A defined quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production a batch must correspond to a defined fraction of the production, characterised by its intended homogeneity. The batch size may be defined either by a fixed quantity or the amount produced in a fixed time interval.

Batch Number (or Lot) Number
A distinctive combination of numbers and/or letters which specifically identify a batch or lot and from which the production history can be determined.

Calibration
The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a traceable standard over an appropriate range of measurements.

Chemical Reaction
A process that involves a chemical transformation of a starting material or intermediate to form a new compound (e.g., bond formation, oxidation. reduction).

Computer System
A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control.

Computerised System
A system including computer system, all sensors, transmitters, actuators and wiring needed to control the process.

Contamination
The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport.

Continuous Production
A process in which a material is continuously produced in a step or series of steps. In a continuous process the batches of raw materials and the process parameters can be statistically but not absolutely, correlated to the material produced in a given window of time.

Critical
A material, process step or process condition, test requirement or any other relevant parameter is considered to be critical when non-compliance with predetermined criteria directly influences the quality attributes of the API in a detrimental manner.

Cross-Contamination
Contamination of a material or product with another material or product..

Drug (or Medicinal) Product
A finished dosage form, for example, a tablet, capsule or solution, that contains one or more APIs, generally, but not necessarily, in association with one or more inactive ingredients.
The term also includes a finished dosage form that does not contain an API but is intended to be used as a placebo.

Enantiomers
Compounds with the same molecular formula as the API, which differ in the spatial arrangement of atoms within the molecule and are non-superimposable mirror images.

Expiry (or Expiration) Date
The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

Extraneous Substance
An impurity arising from any source extraneous to the manufacturing process.

Impurity
Any component of the API which is not the chemical entity defined as the API.

Identified Impurity
An impurity for which a structural characterisation has been achieved.

Unidentified Impurity
An impurity which is defined solely by qualitative analytical properties (e.g., chromatographic retention time).

Impurity Profile
A description of the identified and unidentified impurities present in the API.

In-Process Control
Testing performed during production to monitor and, if necessary, to adjust the process.

Intermediate
A material produced during steps of the synthesis of an API which must undergo further molecular change before it becomes an API.

Lot
See batch

Manufacture
All operations of purchase of materials, production, quality control, release, storage, and distribution of APIs and the related controls.

Methods Validation
The process by which it is established, by laboratory studies, that the performance characteristics of the method meet the requirements for the intended analytical applications.

Mother Liquor
The residual saturated liquid which remains after the crystallisation of a liquid. A mother liquor may contain unrecovered products (i.e., unreacted starting materials, intermediates, trace levels of the API and/or impurities).

New Molecular Entity
The designated therapeutic molecular entity which has not been approved for (also referred to as a new chemical entity or new drug substance). It may be a complex, simple ester, or salt of a previously approved API.

Objectional Contamination
Objectionable contamination is any contamination which alters the safety, identity, strength, quality, or purity of the API or intermediate beyond the official or other established requirements.

Packaging Material
Any material used to protect an API during storage and transport but excluding labels.

Physical Manipulation
A process other than a chemical reaction that may change the purity or the physical properties of the material, including but not limited to, crystallisation, recrystallisation, gel filtration, chromatography, milling, drying, or blending.

Polymorphism
The occurrence of different crystalline forms of the same API.

Potential Impurity
An impurity which, from theoretical considerations, may arise from or during manufacture. It may or may not actually appear in the API.

Primary Reference Standard
A particular batch of an API or intermediate specifically prepared by independent synthesis or by further purification of existing production material, and shown, by an extensive set of analytical tests, to be authentic material of the highest purity.

Process Validation
Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality characteristics.

Procedures
Description of the operations to be performed, the precautions to be taken, and measures to be applied related to the manufacture of an API.

Purification Procedure
A process, such as crystallisation distillation or chromatography, intended to improve the purity of an intermediate or of an API.

Production
All operations involved in obtaining an API, from the receipt of materials through processing to packaging and labelling.

Qualification
The action of proving that any equipment works correctly and consistently and produces the expected results. Qualification is part of, but not limited to, a validation process, i.e., installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ).

Quality Assurance
The sum total of the organised arrangements made with the object of ensuring that all APIs are of the quality required for their intended use.

Quality Control Unit
An organisational unit with defined responsibilities and authority for controlling, through checking or testing, that specifications are met and quality systems are maintained.

Quarantine
The status of materials isolated physically or by other effective means pending a decision on their subsequent use.

Raw Material
Any ingredient intended for use in the production of APIs. These include starting materials, intermediates, process aids, and solvents.

Reagent
A substance, other than the starting material or solvent, which is used in the manufacture of an API or intermediate.

Recovery
Any treatment of materials by a process intended to make them suitable for further use.

Reprocessing
Introducing an intermediate or API that does not conform to standards or specifications, back into the process and repeating step(s) that are part of the established manufacturing process (e.g., recrystallizing using the same solvent).

Retest Date
The date when samples of the API should be re-examined to ensure that material is still suitable for use.

Retest Period
The period of time during which the API can be considered to remain within specifications, and therefore acceptable for use in the manufacture of a given drug product, provided that it has been stored under defined conditions. After this period, the batch should be retested for compliance with specifications and then used immediately.

Reworking
Subjecting an intermediate or API that does not conform to standards or specifications, to processing step(s) that are different from the established manufacturing process (e.g., recrystallizing with a different solvent).

Solvent
An inorganic or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of an API or intermediate.

Starting Material
A material used in the synthesis of an API which is incorporated as an element into the structure of an intermediate and/or of the API. Starting materials are normally commercially available and of defined chemical and physical properties and structure.

Validation
A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria.

Validation Protocol
A written plan stating how validation will be conducted. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics. sampling and test data to be collected, number of validation runs, and acceptable test results.

Working Standard
An API or intermediate of established quality and purity, as shown by comparison to a primary reference standard, used as a reference substance for routine laboratory analysis.

Actual Yield
The quantity that is actually produced at any appropriate phase of manufacture, processing, or packing of a particular API or intermediate.

Expected Yield
The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on the historical data of a process.

Theoretical Yield
The quantity that would be produced at any appropriate phase of manufacture, processing, or packing of a particular API or intermediate, based upon the quantity of components to be used, in the absence of any loss or error in actual production.

2 Quality Management

2.1 Principle

2.10 Quality Management is an important management function that determines and implements the quality policy of an API manufacturer.

2.11 The basic element of quality management is an appropriate quality system, encompassing the organizational structure, procedures, processes and resources, as well as systematic actions necessary to ensure adequate confidence that an API will satisfy the established specifications for purity, identity, safety and quality.

2.12 The management with executive responsibility should define and document its policy for quality, including objectives for quality and its commitment to quality. The responsibility, authority and relations between persons who have an impact on the quality of APIs should be specified.

2.13 The preparation of a Quality Manual is recommended as a key to the achievement of an appropriate quality system.

2.2 Quality Assurance

2.20 All quality related activities should be based on sound scientific evidence and should be carried out in a systematic and appropriate manner as reflected in this document.

2.21 Written procedures should be established covering all these activities. The procedures should be clear and detailed and they should be followed.

2.22 All quality related activities should be documented.

2.23 Any deviation from established procedures should be documented and investigated. Such investigation should determine whether the deviation had an impact on intermediate or API quality. The results of such investigation should be reviewed and approved by the Quality Control Unit.

2.24 Procedures should be established to ensure that the designated officials of the firm, if they are not personally involved in, or immediately aware of such actions, are notified

in writing of any investigations conducted, any recalls, reports of inspectional observations issued by the Regulatory Authority, or any regulatory actions relating to CGMPs initiated by a regulatory authority with respect to the company's operation.

2.3 Application of CGMP Principles and Controls

2.30 API manufacturers should apply current good manufacturing practice (CGMP) to all steps in the manufacturing process, beginning with the use of starting materials, and validate critical process steps.

2.31 The stringency of controls, such as the extent of written procedures, in process controls, sampling, testing, monitoring, validation, and documentation should increase as the process proceeds from early intermediate stages to final synthesis and purification stages.

2.4 Internal Audits and Annual Product Quality Reviews

2.40 The Quality Control Unit should have responsibility and authority for managing and reviewing periodic internal audits in order to monitor the implementation and the compliance with the requirements of Quality Assurance and current good manufacturing practice and to propose necessary corrective actions.

2.41 The findings and the corrective actions should be documented.

2.42 Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least:

- A review of in-process control and final product test results;
- A review of all products which failed to meet established specifications;
- A review of all processes which failed to perform as expected;
- A review of any changes carried out to the processes;
- A review of on-going stability studies;
- A review of all complaints and recalls;
- A review of adequacy of corrected actions;
- A review of the necessity of revalidation.

3 Quality Control

3.1 Quality Control Unit

3.10 There should be a Quality Control Unit, independent of the Production.

3.11 The Quality Control Unit should be involved in all quality related matters.

3.12 The Quality Control Unit should review and approve all quality related issues.

3.13 The Quality Control Unit should have adequate analytical control facilities at its disposal. The quality control unit may delegate the responsibility and authority for testing and release of intermediates to in-process laboratories reporting to the manufacturing department.

3.14 The responsibilities of Quality Control Unit should be described in writing, and should include but not necessarily be limited to responsibility for:

- Approving specifications;
- Approving test procedures, including in process controls;
- Approving validation plans, protocols and reports;
- Review of changes in product, process, or equipment, to determine if revalidation is warranted;
- Approval of changes to specifications, sampling plans and test procedures;
- Sampling procedures;
- Approving reference standards;
- Analytical investigations and evaluation of results;
- Testing materials;
- Providing analytical reports;
- Approving or rejecting intermediates and APIs manufactured, processed, packed, or held under contract by another company;
- Gathering data to support retest dates (stability testing);
- Evaluation and approval of contractors;
- Review of batch records;
- Review of complaints;
- Use of materials not meeting specification;
- Use of returned material;
- Internal and external audits;
- Performing periodic assessments of procedures, policies, and responsibilities within the company’s manufacturing and control operations.

3.2 Specifications

3.20 Specifications should be available for all materials. They should be approved by the Quality Control Unit.

3.21 A system should be in place to determine conformance to appropriate written specifications for the acceptance of all materials.

3.22 Impurity profiles should be established for each API.

4 Personnel

4.1 Personnel Qualifications

4.10 There should be an adequate number of personnel appropriately qualified to perform and supervise API manufacturing, processing, holding, or quality control activities.

4.11 The personnel and their supervisors should be qualified by appropriate education, training and experience to perform their assigned duties.

4.12 The responsibilities and authority of the key personnel should be specified in writing.

4.13 Training should be regularly conducted by qualified individuals. Records of training should be maintained and its effectiveness evaluated.

4.14 Training should extend to the particular operations that the employee performs and current good manufacturing practice as they relate to the employee's functions.

4.2 Personnel Hygiene

4.20 Personnel should practice good sanitation and health habits.

4.21 Clean Protective apparel, such as head, face, hand, and arm coverings, should be worn as necessary, to protect APIs and intermediates from contamination.

4.22 Personnel should avoid direct contact with APIs.

4.23 Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the production or control areas.

4.24 Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities which could result in compromising the quality of APIs. All personnel should be instructed to report such health conditions to supervisory personnel.

4.25 Only personnel authorised by supervisory personnel should enter those areas of the buildings and facilities designated as limited-access area.

4.3 Consultants

4.30 Consultants advising on the manufacture and control of intermediates or APIs should have sufficient education, training, and experience, or any combination thereof to advise on the subject for which they are retained.

4.31 Records should be maintained stating the name, address qualifications, and type of service provided by all consultants.

5 Buildings and Facilities

5.1 Design and Construction

5.10 Any building used in the manufacture, processing, packing, or holding of APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations

5.11 Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.

5.12 Where the equipment itself (i.e., closed systems) provides adequate protection of the product, such equipment may be located outdoors

5.13 The flow of raw materials, intermediates, and APIs through the building or buildings should be designed to prevent mix-ups or contamination.

5.14 There should be defined areas for the following activities:

- Receipt, identification, storage, and withholding from use of raw materials or intermediates, pending release;
- Sampling of incoming raw and intermediate materials;
- Holding rejected raw materials, intermediates and APIs before disposition;
- Storage of released raw materials intermediates, and APIs;
- Manufacturing and processing operations;
- Packaging and labelling operations;
- Quarantine storage before release of intermediates and APIs;
- Control and laboratory operations.

5.15 Adequate facilities for changing clothes and for washing, toilets, rest rooms and refreshment rooms should be available and should be separate from the production areas.

5.16 Facilities should also be designed to limit exposure to objectionable microbiological contaminants.

5.17 Laboratory areas should be normally separated from production areas. Some laboratory areas, in particular those used for in-process controls, may be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements.

5.2 Utilities

5.20 All utilities should meet specifications appropriate for their intended use.

5.21 Critical utilities (such as process air and water systems) should be regularly monitored to ensure that specifications are met and action is taken when limits are exceeded.

5.22 Adequate ventilation should be provided and should include equipment for control of air pressure, microorganisms, dust, humidity, and temperature, where appropriate

5.23 Where APIs are handled or exposed to the production environment, these areas should be provided with adequate air filtration, dust collection and exhaust systems to control airborne contaminants and prevent cross contamination.

5.24 If air is recirculated to production areas, appropriate measures should be taken to control contamination and cross-contamination

5.25 Permanently installed pipework should be labelled to indicate the contents and the direction of flow. Pipework should be located so that rust, condensate on the surfaces, or leakages will not result in the contamination of the API.

5.26 Drains should be of adequate size and should be provided with a suitable device to prevent back-siphonage.

5.3 Water

5.30 Water and steam used in the manufacture of APIs should be demonstrated as suitable for its intended use and should not adversely alter API quality.

5.31 If steam is injected directly into the process it should meet an appropriate and approved specification.

5.32 Water used in early processing steps should, at a minimum, meet national standards for potable water. In the absence of national standards, WHO standards should be used.

5.33 Tighter chemical and microbial quality specifications are necessary for water used during critical process steps, such as final isolation and crystallization, or during early processing steps if impurities that affect API quality are present in the water and cannot be removed in later steps. If the API needs to be of a high microbiological purity, appropriate action limits for total microbial counts, objectionable organisms and endotoxins may need to be established and met.

5.34 Where water is treated to achieve an established quality, the treatment process should be validated and monitored.

5.35 Water used in the final isolation and purification steps of a non-sterile API intended for parenteral products should be monitored and controlled for bioburden and endotoxins.

5.36 Process water should be supplied under continuous positive pressure in a plumbing system free of defects.

5.4 Containment

5.40 Dedicated production facilities, including dedicated air handling, water and process equipment should be used for the production of each sensitising API such as penicillins and cephalosporins. Appropriate measures should be established and implemented to prevent cross-contamination from personnel moving from one dedicated area to another.

5.41 Dedicated facilities should also be considered for other APIs of high pharmacological activity or toxicity, such as certain steroids or cytotoxic anti-cancer agents.

5.5 Security

5.50 There should be a plant security system in operation to prevent unauthorised persons gaining access to the facilities.

6 Process Equipment

6.1 Design and Construction

6.10 Equipment used in the manufacture, processing, packing, or holding of intermediates and APIs should be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.

6.11 Equipment should be constructed so that surfaces that primary contact surfaces for raw materials, intermediates, or APIs are not reactive, additive or absorptive and do not alter the quality of the intermediates and APIs.

6.12 Any substances required for the operation of equipment, such as lubricants or coolants, should not contact raw materials, intermediates, or APIs so as to alter the quality of intermediates and APIs beyond the official or other established specifications. Food grade lubricants and oils should be used whenever there is a risk of contamination of APIs.

6.13 Where feasible, equipment design, construction, and installation should allow for ease of cleaning, and as applicable, sterilization.

6.14 Closed equipment should be used when feasible. When open equipment is used, or equipment is opened, care should be taken to avoid contamination.

6.15 A set of as-built drawings should be maintained for equipment, computers, and instrumentation.

6.2 Equipment Maintenance and Cleaning

6.20 Written procedures should be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of intermediates and APIs. These procedures should include, but should not be limited to the following:

- Assignment of responsibility for cleaning and maintaining equipment;
- Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;
- A complete description of the methods and materials including dilution of cleaning agents, used to clean and maintain equipment, and when necessary, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning and maintenance;
- Removal or obliteration of previous batch identification;
- Protection of clean equipment from contamination prior to use;
- Inspection of equipment for cleanliness immediately before use, if practical;
- Establishing the maximum times that may elapse between the completion of processing and equipment cleaning.

6.21 Equipment, including utensils and storage vessels, should be cleaned as appropriate to prevent contamination and carry over of degraded material that would alter the quality or purity of the intermediate or API beyond the official or other established specifications. In general, cleaning efforts should be directed to situations or process steps where contamination or incidental carryover poses the greatest risk.

6.22 Where equipment is dedicated to production of successive batches of the same intermediate or API, equipment should be evaluated for cleanliness between successive batches, using worst-case scenarios (e.g. weekend carryover), to prevent objectionable carryover of contaminants or degradants. As processing approaches the final purified API it is important to ensure that incidental carryover between batches does not adversely impact on the established impurity profile.

6.23 Proper cleaning of non dedicated equipment between products is important to prevent cross contamination. If cleaning of a specific type of equipment is difficult, the equipment may need to be dedicated to a particular intermediate or API.

6.24 The choice of cleaning methods, cleaning agents, and levels of cleaning should be defined and justified. Selection of cleaning agents (e.g., solvents) should depend on:

- The cleaning agent's ability to remove residues of raw materials, intermediates, precursors, degradation products and isomers;
- Whether the cleaning agent leaves a residue itself;
- Compatibility with equipment construction materials.

6.3 Cleaning Validation

6.30 When appropriate, cleaning methods should be validated. In general, cleaning validation should be directed to situations or process steps where contamination or cross-contamination, or incidental carryover of degradants pose the greatest–risk to product quality.

6.31 The validation protocol should clearly describe the equipment to be cleaned, specifying critical parts, methods, materials and scope of cleaning, parameters to be monitored and controlled, acceptance criteria, location and size of samples, procedures for collecting samples, and analytical methods and responsible persons for conducting the work.

6.32 If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a worst-case product may be selected to represent all products for purposes of cleaning validation. The worst-case selection may be based on scientific justification and can be a combination of potency, toxicity, solubility, stability, or difficulty of cleaning. The sensitivity of the analytical method could be a limiting factor when selecting the worst case product or group of products.

6.33 The acceptable level of cleanliness obtained from a cleaning method should be based on sound scientific evidence.

6.34 The hardest areas to clean on the equipment and the type of equipment surface to be cleaned should be considered when sampling methods are developed. Sampling methods should generally include swabbing and rinsing or other alternative methods (i.e. direct extraction) to detect both insoluble and soluble residues.

6.35 Validated analytical methods having specificity and sensitivity to detect residuals or contaminants should be in place. The detection limit for each analytical method should be sufficiently sensitive to detect the acceptable level of the residue or the contaminant.

6.36 Residue limits should be practical, achievable, and verifiable and should be based on the most deleterious residual component. A method of setting limits may include establishing a limit that is based on the minimum known pharmacological or physiological activity of the API or its most deleterious component

6.37 As appropriate, cleaning/sanitization studies should address microbiological contamination for APIs and intermediate processes for which microbiological contamination is a concern.

6.38 The method's attainable recovery level should be established.

6.39 Cleaning procedures should be monitored after validation to ensure that these procedures are effective when used during routine production.

6.4 Calibration

6.40 Control, monitoring and test equipment that is critical for assuring the quality of the final API should be routinely calibrated according to written procedures.

6.41 Equipment calibrations should be performed using standards traceable to certified standards.

6.42 Records of those calibrations should be maintained.

6.43 The current calibration status of the equipment should be apparent.

6.44 Instruments that do not meet calibration criteria should not be used.

6.45 Deviations from approved standards of calibration should be investigated to determine if these could have had an impact on the quality of the final API.

6.5 Computerised Systems

6.50 Automatic, mechanical, or electronic processing equipment or other types of equipment, including computers should be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections should be maintained. Documentation should describe the objective and scope of the system, location of the application, interaction with other systems, and maintenance.

6.51 Appropriate installation qualification (IQ) and operational qualification (OQ) should demonstrate the suitability of computer hardware and software to perform assigned tasks.

6.52 All computerised systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerised application. Public-domain software that has been qualified, does not require the same level of testing.

6.53 If an existing system was not validated at time of installation, a retrospective validation may be carried out if adequate documentation is available.

6.54 All computerised systems should have sufficient controls to prevent unauthorised access or changes to data software and computer hardware.

6.55 Written procedures should be available at least:

- For operating the system;
- To be followed in cases of malfunctioning;
- For detecting and recording errors, and enabling corrections to be made;
- For restarting and data recovery;
- For authorising and carrying out changes;
- For recording changes;
- For electronic signatures.

6.56 Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This may be done by a second operator or by the system itself.

6.57 Incidents which could affect the quality of APIs or the reliability of records or test results should be recorded and investigated.

6.58 All changes made to the computerised system should be formally authorised, documented and tested. Records should be kept of all changes including modifications and enhancements made to the hardware, software and any other critical component of the system to demonstrate that the final system is maintained in a validated state.

6.59 All changes should be approved by the Quality Control Unit.

6.60 If system breakdowns or failures would result in the permanent loss of critical records then a back-up system should be provided.

7 Documentation

7.1 Documentation System

7.10 A system should be established for retaining all appropriate documents, such as development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records.

7.11 Records should be maintained for all components and API containers for at least one year after the expiry date of the batch. For API with retest dates, records should be retained for three years after the batch is completely distributed

7.12 All records or copies of such records, should be readily available for authorised inspection and copying by the Regulatory Authority during the retention period at the establishment where the activities described in such records occurred. These records or copies of them should be subject to photocopying or other means of reproduction as

part of such inspection. Records that can be promptly retrieved from another location by electronic or other means are acceptable.

7.13 Records may be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques, such as microfilming or electronic records, are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.

7.14 Written records should be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each API to determine the need for changes in specifications or manufacturing or control procedures. Written procedures should be established and followed for such evaluations and should include provisions for:

- Review of a representative number of batches, whether approved or rejected, and the records associated with the batch;
- A review of a representative number of batches produced during the evaluation period, whether approved or rejected, and the records associated with the batch;
- A review of process changes, stability data/protocols, complaints, recalls, returned or salvaged APIs and deviation investigations.

7.2 Equipment Cleaning and Use Record

7.20 A written record should be maintained of major equipment cleaning and maintenance (except routine maintenance such as lubrication and adjustments), that shows the date, time, product, and batch number of each batch processed.

7.21 If equipment is dedicated to manufacturing one product, then individual equipment records are not necessary if batches of such products follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use may be part of the batch record or may be maintained separately. The persons performing and checking the cleaning and maintenance should date/sign or initial the record showing that the work was done. Entries in the record should be in chronological order.

7.3 Raw Materials, Intermediates, API Packaging Materials, and Labelling Records

7.30 These records should include the following:

- The identity and quantity of each shipment of each batch of raw materials, intermediates, API packaging materials and labels, the name of the supplier; the supplier's control number(s) if known; the receiving code, and the date of receipt. The name and location of the prime manufacturer, if different from the supplier, should be listed if appropriate, to ensure API quality;
- The results of any test or examination performed and the conclusions derived from this;

- An individual inventory record system for reconciliation of raw materials and intermediates, if appropriate;
- Documentation of the examination and review of labelling and API containers for conformity with established specifications;
- The disposition of rejected raw materials, intermediates, API packaging materials and labels.

7.4 Master Production and Control Records

7.40 To ensure uniformity from batch to batch, master production and control records for each API and intermediate, including each batch size thereof, should be prepared, dated, and signed (full hand-written signature or electronic equivalent) by one person and independently checked, dated, and signed by at least one other person. The preparation of master production and control records should be described in a written procedure and should be followed.

7.41 Master production and control records should include:

- The name of the API or intermediate and an identifying reference code, if applicable;
- A complete list of raw materials or intermediates designated by names or codes sufficiently specific to identify any special quality characteristics;
- An accurate statement of the quantity and unit of measure of each raw material or intermediate using the same weight system (metric, avoirdupois, or apothecary). Reasonable variations may be permitted provided they are justified;
- The manufacturing location and production equipment to be used;
- A statement of expected weight or measure at appropriate phases of processing;
- A statement of expected yields at appropriate phases of processing, including the maximum and minimum percentages of expected yields beyond which investigation is initiated;
- The requirements for storage of the API or intermediates, including the container, labelling, and special storage conditions, if applicable;
- Complete manufacturing and control instructions and, where appropriate, special notations and precautions to be followed, or cross-references to these;
- Any sampling instructions and in-process controls with their limits, where appropriate.

7.5 Batch Production and Control Records

7.50 Batch production and control records should be prepared for each batch of intermediate and API and include complete information relating to the production and control of each batch.

7.51 These records should include an accurate reproduction or reference to the appropriate master production and control record, checked for accuracy, dated and signed (hand-written signature or electronic equivalent).

7.52 Documentation that each significant step in the manufacture, control and packaging of the batch was accomplished should include:

- Dates;
- Identity of individual major equipment;
- Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacture;
- In-process and laboratory control results;
- A statement of the actual yield compared against an expected yield at appropriate phases of manufacture;
- Description of API and intermediate and API packaging;
- Complete label control records, including specimens or copies of labels used for all API batches;
- Any sampling performed;
- Signatures of the persons performing and directly supervising or checking each significant step in the operation;
- Any deviation investigations conducted and their results or reference to that investigation if stored separately;
- Results of release testing.

7.53 Records of analytical tests should be kept, including the preparation, testing and standardisation of laboratory reference standards, reagents, and standard solutions.

7.54 Complete records should be maintained of any modification of an established analytical method. Such records should include the reason for the modification and data to verify that the modification produces results that are as accurate and reliable as the established method.

7.55 Laboratory records should include complete data derived from all tests necessary to ensure compliance with established specifications and standards, including examinations and assays, as follows:

a. A description of samples received for testing with identification of the source (i.e., location from where sample was obtained) quantity, batch number or other distinctive code, date sample was taken, and dates the sample was received for testing.
b. A statement of each method used in testing the sample. The statement identifies the data and/or; source that documents the validity of sample test methods to meet proper standards of accuracy and reliability.

c. If the method employed is in the officially recognised pharmacopoeia, in other recognised standard references, or in other equivalent document and the referenced method is not modified, a statement showing the method and reference will suffice.
d. The suitability of all testing methods used should be verified under actual condition of use.
e. A statement of the weight or measure of the sample used for each test, where appropriate.
f. A complete record of all data secured during each test, including all, and spectra from laboratory instrumentation, properly identified to show the specific component, intermediate, API, or in-process material and batch tested.
g. A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors.
h. A statement of the test results and how they compare with established standards of identity, strength, quality and purity for the component, intermediate, API, or in-process material tested.
i. The initials or signature of the person who performs each test and the date(s) the tests were performed.
j. The initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

7.56 Batch records should be reviewed by the Quality Control Unit to determine conformance with all established, approved written procedures and specifications before a batch is released or distributed.

7.57 Any production, control, or distribution record specifically associated with a batch of API should be retained for at least one year after the expiry date of the batch. For API with retest dates, records should be retained for three years after the batch is completely distributed.

7.58 When computer systems are used to initiate, monitor, adjust, and otherwise control the process, hard-copy batch production records may not be necessary

7.6 Production Record Review

7.60 Batch production and control records for critical process steps should be reviewed and approved by the Quality Control Unit to determine compliance of the API with all established, approved written procedures and specifications before a batch is released or distributed. Production and control records for earlier, non-critical process steps may be reviewed by qualified production personnel or other units following procedures approved by the Quality Control Unit.

7.61 Written procedures should be established and followed requiring the thorough investigation of unexplained discrepancies or the failure of a batch or any of its raw materials or in-process materials to meet specifications (including out-of-specification test result), whether or not the batch has already been distributed. The investigation should extend to other batches of the same API and other APIs that may have been

associated with the specific failure or discrepancy:

- Procedures to identify the cause of the failure or discrepancy;
- Criteria for assigning out-of-specification results to sampling or laboratory error;
- Scientifically sound and appropriate procedures and criteria for excluding any test data found invalid due to a laboratory or sampling error;
- Scientifically sound and appropriate criteria for additional sampling and testing, if necessary, during the investigation;
- Procedures and criteria for extending the investigation to other batches of intermediates or API;
- Procedures for the Quality Control Unit's review and evaluation of the investigation, including all test results, to ensure a thorough investigation;
- Criteria for approving or rejecting batches involved, and for taking action on other batches and products if suggested by the investigation.

7.62 Written record of the investigation should be prepared and should include:

- The reason for the investigation;
- A report summarising the investigation conducted, including all laboratory tests;
- The results of the investigation, including all laboratory test results involved in the investigation;
- Scientifically sound and appropriate justification for excluding any out-of-specification laboratory result found invalid;
- If laboratory results are found invalid, the subsequent laboratory results supporting the final determination of conformity to all appropriate specifications for acceptance;
- The conclusions and subsequent actions concerning all batches of intermediates and API that may have been associated with the failure or discrepancy;
- The signature(s) and date(s) of the person(s) responsible for approving the record of investigation;
- The signature(s) and date(s) of the person(s) responsible for the final decision on disposition of the batch, and on other batches and products involved.

7.63 Any unexplained discrepancy (including a percentage of expected yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch to meet any of its specifications should be thoroughly investigated.

8 Materials Management

8.1 Purchasing

8.10 There should be written procedures describing the purchase, receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of raw materials. Such procedures should be followed.

8.11 Raw materials should be purchased against an agreed specification from an approved supplier or suppliers. The specifications should reflect the ability of the process to remove undesirable impurities and include the knowledge gained during process developments as to critical properties of the raw materials.

8.12 If there is adequate evidence that the supplier can reproducibly provide material meeting the specification, such evidence, such as past quality history, may be used to reduce the amount of in-house testing carried out on raw materials by using Certificates of Analysis from the supplier. However, as a minimum, the identity of each batch of raw materials should be confirmed.

8.13 Manufacturers of APIs should have a system for evaluating the suppliers of critical raw materials.

8.14 Changing the source of supply of critical raw materials should be treated according to Chapter 13, Change Control.

8.2 Receipt and Quarantine

8.20 Upon receipt and before acceptance, each container or grouping of containers of raw materials, should be examined visually for correct labeling, container damage, broken seals, tampering, and potential contaminants.

8.21 Before incoming materials are mixed with existing stocks, e.g. solvents or stocks in silos, they should have been released and procedures should be available to prevent discharging into the wrong stock.

8.22 If bulk deliveries are made in non-dedicated tank trucks, there should be written evidence that cleaning of the tank was conducted before loading the material.

8.23 Each container or grouping of containers (batches) of raw materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify each batch’s status. Large storage containers, and their attendant manifolds, filling, and discharge lines, should be appropriately identified.

8.3 Sampling and Testing of Materials

8.30 Each batch of materials should be tested and released for use, or rejected.

8.31 The number of containers or items to be sampled and the amount of material to be taken from each container should be based on scientific criteria.

8.32 Sampling should be conducted in an area and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

8.33 Containers from which samples are withdrawn should be opened carefully, and subsequently resealed. They should be marked to indicate that a sample has been taken.

8.34 At least one test should be conducted to verify the identity of each raw material.

8.35 Full testing should be done if no reliable certificate of analysis is available. Reliability of certificates of analysis should be checked at regular intervals.

8.36 Hazardous or highly toxic raw materials do not need to be tested provided a valid certificate of analysis is obtained showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials.

8.37 Raw materials should be re-tested and approved or rejected as necessary, after storage for a defined period or after exposure to conditions that might adversely affect the raw material.

8.38 Raw materials in large storage containers should be re-evaluated at defined intervals.

8.39 Each batch of recovered solvent should be tested before use against appropriate specifications, considering the originating process and the intended subsequent use.

8.4 Storage

8.40 Raw materials should be handled and stored in a manner to prevent contamination and cross-contamination

8.41 Bagged or boxed materials should be stored off the floor and suitably spaced to permit cleaning and inspection.

8.42 Certain materials in suitable containers may be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use to prevent contamination.

8.43 Raw materials should be held under quarantine until they have been tested or examined and released by the Quality Control Unit.

8.44 Where appropriate, approved raw materials should be stored in controlled conditions, and rotated so that the oldest stock is used first. Deviation from this requirement is permitted if these are temporary. Raw materials stored under conditions that may have adversely affected their quality should be reevaluated and deemed suitable for use.

8.45 Rejected raw materials should be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

8.5 Retesting of Starting Materials

8.50 Starting materials susceptible to change with time, e.g. hygroscopic or unstable materials, should be allocated a retest period. If such materials are to be used after this period, an evaluation of their properties against the proposed use should be carried out by the Quality Control Unit.

9 Production and In-Process Controls

9.1 Production Operations

9.10 Written procedures should be established and followed for production and process controls, to ensure that APIs or intermediates have the quality they purport or are represented to possess. Such procedures should describe the in-process controls, tests, or examinations to be conducted on in process materials of each step in the process. The specifications, type, and extent of testing may depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted, and the degree to which the process introduces variability in the process.

9.11 Production and process control procedures should be reviewed and approved by the Quality Control Unit and other appropriate organizational units. The procedures should be followed in the execution of the various production and process control functions and should be promptly documented at the time of performance. Deviations from the written procedures should be recorded and explained."

9.12 In process specifications should be derived from research or pilot scale batches or process variability estimates until sufficient process data is collect on full scale production batches.

9.13 Raw materials for intermediate and API manufacturing should be weighed or measured as appropriate to maintain their identity, quality and purity. Measuring devices should be calibrated to ensure accurate results within appropriate ranges. If a substance is subdivided for later use in manufacturing operations, the new container should be suitable and should be identified with the following information:

- Material name and item code;
- Receiving or control number;
- Weight or measure of substance in the new container.

9.14 Critical steps, such as raw materials weighing, measuring, or subdividing operations should be verified. Prior to use, production personnel should verify that the raw materials are those specified in the batch record for the intended API.

9.15 Actual yields and percentages of expected yields should be determined at the conclusion of each appropriate phase of the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale, or manufacturing data. Deviations from expected yield should be investigated to determine releasability of affected batches, and the manufacturing process should be evaluated to minimize the likelihood of reoccurrence.

9.16 Major equipment and permanently installed processing lines used during production of an intermediate or API should be appropriately identified to show their contents. and, when necessary, the manufacturing step for which they are intended to be used. Production records should show the major equipment used in the manufacture of each batch of an intermediate and API.

9.17 Storage time limits and storage conditions for intermediates should be established.

9.18 Materials identified for reprocessing or reworking should be quarantined until the operations are performed.

9.2 In-process Controls

9.20 In-process controls, including the limits (where necessary both warning and action limits), should be fixed in writing.

9.21 Some in process tests may be performed by qualified production department personnel, and the process adjusted without prior quality control approval, provided adjustments are made within limits pre-established and approved by the Quality Control Unit. All tests and results should be fully documented in the batch record.

9.3 Blending Batches

9.30 Blending of batches to ensure batch uniformity and to facilitate processing is acceptable, provided it is adequately controlled and documented.

9.31 The maximum batch size for the final blends should be limited to the maximum working capacity of the largest blender. Any steps, such as drying, combined with the blending step should be performed in equipment designed to ensure blend uniformity.

9.32 Each batch incorporated into the blend should have been manufactured using an approved process and should be individually tested and found to meet appropriate specifications prior to blending.

9.33 The batch number assigned to the final blend should allow traceability back to the individual batches that make up the blend.

9.34 Selective blending of out-of-specification materials with materials meeting specification, with the intention of disguising defects, is not an acceptable practice.

9.35 The physical or chemical characteristics of each batch incorporated into the blend should have not been adversely affected by prolonged storage after manufacture. Appropriate limits on the maximum time allowable between production of individual batches and their blends should be established and followed.

9.36 Blending processes should be validated to show homogeneity of the combined batch. Validation should include testing of critical product attributes that may be affected by the blending process. These may include impurity levels, moisture content, particle size range, and bulk and tap density. The quantity or size of individual samples taken from the blend should be adequate for complete testing and reanalysis if necessary.

9.37 Tailings (i.e., relatively small quantities of material not packaged with the parent batches for reasons unrelated to quality) from different batches blended to form a single batch should come from previously tested and acceptable batches produced by the same process.

9.38 Stability testing of the final blended batches should be conducted. This should include assignment of an expiry date or retest date for the blended batch based on the manufacturing date of the oldest batch in the blend.

9.4 Contamination Control

9.40 Production operations should be conducted in a manner that will prevent contamination of APIs or intermediates by other compounds or extraneous materials.

9.41 Special care should be taken when pure and final APIs are handled.

9.42 For APIs not required to be sterile, written procedures should be established to prevent objectionable microbiological contamination, as appropriate.

9.43 For intermediates and APIs having specified endotoxin limits, written procedures should be established and followed to control endotoxin generation or contamination.

9.44 Any building used in the manufacture of APIs should be maintained in a clean and sanitary condition and should be free of infestation by rodents, birds, insects, and other vermin.

9.45 Waste should be stored and disposed of in a timely and sanitary manner. Containers for waste material should be clearly identified as such.

10 Packaging and Labelling

10.1 General

10.10 There should be written procedures describing the receipt, identification, storage, handling, sampling, examination, and/or testing of API containers, closures, labeling and packaging materials. Such written procedures should be followed.

10.2 Packaging Materials

10.20 Containers and closures should provide adequate protection against external factors in storage that can cause deterioration or contamination of the API.

10.21 Containers and closures should be clean and should not be reactive, additive or absorptive so as to alter the quality of the API beyond the specified limits.

10.22 If returnable containers are re-used, they should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced.

10.23 Labels and packaging materials should be representatively sampled, examined or tested and released before use.

10.3 Packaging and Labelling Operations

10.30 There should be documented procedures designed to ensure that correct packaging materials and labels are used.

10.31 API containers that are shipped outside of the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents have been altered.

10.32 Labels used on containers of APIs shall indicate the name and address of the original manufacturer as well as that of the repacker, relabeller or processor if different.

10.4 Labelling Control

10.40 Access to the storage areas should be limited to authorised personnel.

10.41 Procedures should be used to reconcile the quantities of labels issued, used, and returned.

10.42 The procedures should require evaluation of discrepancies found between the number of containers labelled and the quantity of labels issued. Such discrepancies should be investigated, and the investigation should be approved by the Quality Control Unit.

10.43 All excess labels bearing batch numbers or other batch related printing should be destroyed. Returned labels should be maintained and stored in a manner that prevents mix-ups and provides proper identification.

10.44 Obsolete and out-dated labels should be destroyed.

10.45 Printing devices used to print labels in packaging operations should be monitored to ensure that all imprinting conforms to the print specified in the batch production record.

10.46 Packaged and labelled APIs should be examined to ensure that containers and packages in the batch have the correct label. Results of these examinations should be recorded in the batch production or control records.

10.47 Labeling issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented in the batch production record.

10.48 Each API should be identified with a batch or control number that permits determination of the history of its manufacture and control.

10.49 To prevent mix-ups and contamination there should be physical or spatial separations from other API operations.

10.50 Packaging and labeling facilities should be inspected immediately before use to ensure that all materials have been removed from previous operations. This examination should be documented in the batch production records.

11 Storage and Distribution

11.1 Warehousing Procedures

11.10 Facilities should be available for the storage of all materials under appropriate conditions. Records should be maintained of these conditions if they are critical for the maintenance of product characteristics.

11.11 Unless there is an alternative system to prevent the unintentional or unauthorised use of quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been taken.

11.2 Distribution Procedures

11.20 APIs should not be released for distribution to third parties before the evaluation by the Quality Control Unit has been completed.

11.21 APIs should be shipped in a manner that does not adversely affect their quality.

11.22 Special shipping or storage conditions for an API should be stated on the label and complied with. Such conditions should comply with standard definitions in official pharmacopoeias, or precisely defined storage temperatures should be indicated.

11.23 A system should be in place by which the distribution of each batch of API can be readily determined to facilitate its recall if necessary.

12 Laboratory Controls

12.1 Batch Testing and Release for Distribution

12.10 For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine satisfactory conformance to specifications.

12.11 Any out-of-specification result obtained should be investigated and documented.

12.12 Resampling and retesting should be performed according to a documented procedure. The procedure should require analysis of the data, assessment of whether a significant problem exists and allocation of the tasks for corrective actions. A report of the investigation should be prepared that includes the conclusions and follow-up actions.

12.13 The evaluation of the quality of an API before being released should be based on the results of analytical testing as well as on the evaluation of production conditions, including a review of the batch production records and process deviation reports.

12.14 As appropriate, testing should be performed for organic volatile impurities and other major impurities.

12.15 Appropriate microbiological tests should be concluded on each batch of intermediate and API required to be free of objectionable microorganism.

12.16 Any unexplained discrepancy or the failure of a batch to meet its specifications should be thoroughly investigated. The investigation should extend to other batches of the same intermediate or API and other batches that may have been associated with the specific failure or discrepancy. A written record of the investigation should be prepared that includes the conclusions and the corrective actions to determine root cause.

12.17 No materials should be released or used before the evaluation of the Quality Control Unit has been completed.

12.18 The persons authorised to release final batches should be specified.

12.2 Validation of Analytical Procedures

12.20 The objective of the analytical procedure should be clearly understood.

12.21 The following typical validation characteristics should be considered:

- Accuracy;
- Precision (repeatability and intermediate precision);
- Specificity;
- Detection limit;
- Quantitation limit;
- Linearity;
- Range;
- Ruggedness.

12.3 Certificates of Analysis

12.30 Authentic certificates of analysis should be issued for a specific batch of API.

12.31 Information on the batch number, the date of manufacture, the date of analysis and the expiry or retest date should be provided on the certificate of analysis.

12.32 For each test performed, the requirements including the acceptance limits, and the results obtained should be given.

12.33 Certificates of analysis should be dated and signed by the person responsible for the Quality Control Unit and should be on letterhead paper showing the name, address and telephone number of the original manufacturer. In case the analysis has been carried out by a repacker or reprocessor, the certificate of analysis should be on letterheaded paper showing the name, address and telephone number of the repacker/reprocessor.

12.34 Certificates of analysis carried out by or on behalf of repackers/reprocessors should be on letterheaded paper identifying the laboratory that has carried out the analysis. They should also contain a reference to the name of the original manufacturer and to the original batch certificate, a copy of which should be attached.

12.35 Electronic signatures may be acceptable provided they are authenticated and secure.

12.4 Stability Testing of APIs

12.40 A documented testing program should be designed to assess the stability characteristics of APIs, and the results should he used to determine appropriate storage conditions and retest dates. The testing program should be documented, ongoing and include:

- The number of batches per year, sample size and test intervals;

- Defined and controlled storage conditions (e.g., temperature and humidity) for stability sample;
- Additional stability samples should be stored under stressful conditions (e.g., elevated temperatures, light, humidity, and freezing) if such conditions can be reasonably anticipated during storage and distribution of the API;
- Reliable, meaningful, and specific test methods to adequately assess stability;
- Where appropriate these programmes should be consistent with the ICH Guidelines - Stability testing of APIs and products.

12.41 An adequate number of API batches should be tested, at suitable intervals, to determine an appropriate expiry or retest date, and records should be maintained of such testing.

12.42 Expiry or retest dates and related storage conditions should be derived from long-term stability studies that include at least three batches in the testing program. However, where data from previous studies or from literature shows that the API is expected to remain stable for at least two years, fewer than three batches may be used in the initial testing program.

12.43 Pilot scale batches may be used if (1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale; and (2) the quality of the API represents the material to be made on a commercial scale. If pilot scale batches are used to develop a tentative expiry date, the first three commercial production scale batches manufactured should be placed on long-term stability using the same stability protocol.

12.44 Long-term testing is generally recommended every three months over the first year, every six months over the second year, and yearly afterwards, as appropriate. At least one additional batch should be added to the stability testing program annually.

12.45 APIs having shelf-lives of one year or less, should be tested monthly for the first three months, and at three month intervals after that.

12.46 The test procedures used in stability testing should have been validated and be stability indicating.

12.47 Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in polyliners within fibre drums, stability samples may be packaged in bags of the same material and in smaller-scale drums of similar or identical material composition to the market drums.

12.5 Expiry and Retest Dating

12.50 Where data derived from stability studies demonstrate that an API has a shelf life of less than two years when held under appropriate storage conditions, the labelling should specify an appropriate expiry date or retest date.

12.51 Expiry or retest dates should relate to any storage conditions stated on the labels, and should be supported by appropriate stability studies

12.52 In the case of antibiotic and biological APIs an expiry date only should be specified.

12.6 Reserve/Retention Samples

12.60 Appropriately identified reserve samples of each API batch should be retained for one year after the expiration date or retest date of the batch assigned by the manufacturer or for three years after distribution of the batch.

12.61 The reserve sample should be stored under conditions consistent with product labels, in the same packaging system in which the API is stored or in one that is equivalent to the marketed packaging system. Sufficient quantities should be retained to conduct at least two full compendial analysis.

12.62 Representative reserve samples should be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve samples. Any evidence of deterioration should be investigated. The results of the examination should be recorded and maintained with other stability data on the API.

13 Validation

13.1 Validation Policy

13.10 The company's overall policy, intentions and approach to validation, including the validation of production processes, cleaning methods, analytical test methods and computerised systems, should be established in the Validation Master Plan.

13.11 Fully validated analytical methods should be used for process and cleaning validation studies.

13.12 The critical process parameters should be identified during the development stage, and the ranges necessary for the reproducible operation of the process should be defined.

13.13 Validation should extend to those process steps determined to be critical to the quality and purity of the final API, and should include:

- Definition of the API in terms of its critical product attributes. Attributes to be considered should include chemical purity, qualitative and quantitative impurity profiles, physical characteristics such as particle size, bulk/tap density, polymorphic forms, moisture and solvent content, homogeneity, and microbial quality (if the product is susceptible to microbial contamination);

- Identification of process parameters that may affect the critical quality attributes of the API. Critical parameters should be determined by scientific judgment, and should typically be based on knowledge derived from research, scale-up batches, or manufacturing experiences:
- Data to substantiate the ranges for critical process parameters should generally be obtained from laboratory or pilot scale batches, unless a specific parameter can only be evaluated on a production scale;
- Examples of processing steps that may be defined as critical include, but are not limited to: phase changes, such as dissolution or crystallization; phase separation, such as filtration or centrifugation; steps that cause chemical changes; steps that alter temperature or pH; mixing of multiple components; and , steps that cause changes in surface area, particle size, bulk and tap density or homogeneity;
- Critical process steps and parameters to control and monitor should be defined by the manufacturer using appropriate studies. These may include, but are not limited to reaction times, reaction temperatures, reactant ratios, concentrations, pressures, pH, and yields;
- Confirming impurity profiles is an important aspect of process validation. In principle, process validation should provide conclusive evidence that the levels of contaminants are reduced in purification steps.

13.2 Validation Documentation

13.20 A specific Validation Protocol should be established that specifies how validation of a particular process will be conducted.

13.21 The Validation Protocol should identify who is responsible for design, review, approval and documentation of each validation phase.

13.22 The Validation Protocol should identify the quality of materials used in the process (e.g., recovered vs. fresh solvents, etc.), processing equipment, critical process parameters, operating ranges, the sampling plan, test data to be collected, and the acceptance criteria.

13.23 The Validation Protocol should specify the type of validation to be conducted (e.g., prospective, concurrent, or retrospective), and the number of process runs. The number of process runs should depend on the extent of validation and complexity of the process or the importance of any process change under consideration.

13.24 The Validation Protocol should be approved by the Quality Control Unit.

13.25 On completion of the validation work a Validation Report, cross-referencing the Validation Master Plan and the Validation Protocol, should be drawn up, summarising the results obtained, commenting on any deviations observed, and drawing the necessary conclusions.

13.26 Should the results of the validation not provide sufficient evidence that the process is valid, then the report should propose changes which should be made to the facilities, equipment, utilities or process to correct the noted deficiencies.

13.3 Process Validation

13.30 Process validation activities should be subdivided as follows:

- Design Qualification (DQ) in which the proposed design of the facilities, equipment or systems is documented as being suitable for the intended purpose;
- Installation Qualification (IQ) in which evidence is gathered and recorded that the facilities, equipment or systems as installed or modified, comply with the approved design and the manufacturers recommendations;
- Operational Qualification (OQ) in which evidence is gathered and recorded that the facilities, equipment or systems as installed or modified, perform as intended throughout the anticipated operating ranges;
- Performance Qualification (PQ) in which the performance is verified.

13.31 The instruments used to measure critical parameters should be calibrated and facilities, utilities and systems should be qualified before process validation is commenced.

13.32 Prospective validation should be performed for new or substantially modified API processes.

13.33 Concurrent validation may be conducted for processes or products that are run infrequently. These batches may be released prior to the completion of all process validation based on thorough monitoring and testing of batches.

13.34 Retrospective validation is acceptable for well established processes that have been used without significant changes in raw materials, equipment, systems, facilities or the production process.

13.35 Retrospective validation is possible only if:

- Critical product attributes and critical process parameters have been identified and documented;
- appropriate in-process specifications and controls have been established and documented;
- There have not been excessive process/product failure attributable to any cause other than operator error or equipment failure unrelated to equipment suitability;
- impurity profiles have been established for the existing API;
- in-process and end product test data show batch to batch consistency.

13.36 Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications.

13.37 Retrospective validation should include examination of a sufficient number of batches (at least 10 to 30 consecutive batches) to demonstrate process consistency. Additional testing of retained samples and the production of new batches may be needed to obtain the necessary amount or type of data required to validate the process.

13.4 Revalidation

13.40 Processes should be periodically re-evaluated to verify that they are still operating in a valid manner.

14 Change Control

14.00 To ensure a continued state of process control, a formal change control system should be established that is designed to evaluate all changes that may affect the production and control of the API or intermediate. Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, facilities, support systems, equipment (including computer hardware), processing steps, and packaging materials, and computer software. Any changes should be drafted, reviewed, and approved by the appropriate organizational units, and reviewed and approved by the Quality Control Unit.

14.01 The change-control program may provide for a classification scheme to evaluate changes in raw materials, manufacturing sites, scale of manufacturing, manufacturing equipment, and production processes. This classification procedure can help in determining what level of testing, validation, and documentation is needed to justify changes to a validated process. Changes may be categorized as minor or major or by categories (e.g., Levels 1 - 2) depending on the nature and extent of the changes, and the effects these changes may impart on the process. In all cases, scientific judgment should determine what additional testing and validation studies are needed to justify a change in a validated process.

14.02 A minor change could is defined as one that is unlikely to have a detectable impact on the critical attributes of the API. Such changes would not shift the process in any discernible manner, and may be implemented with minimal or no testing and validation. For example, "like-for-like" equipment replacements where equipment is repaired to its initial validation state or in which identical or similar equipment is introduced into the process, would be unlikely to affect the process if adequately installed and qualified.

14.03 A major change would be likely to have a significant impact on the critical quality attributes of the API. For example, a change in solvent used for the final crystallization could have a significant impact on the impurity profile, physical attributes, and other critical attributes of the API. Such changes would warrant major testing and suitable revalidation studies to justify the changes.

14.04 When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.

14.05 After the change has been implemented, there should be a careful evaluation of the first batches produced or tested under the change.

14.06 The potential effects of critical process changes upon established retest or expiry dates should be monitored by adding samples made by the modified process to the accelerated and real time stability programme.

14.07 Current dosage form manufacturers should be notified of changes from established production and process control procedures.

15 Rejection and Re-Use of Materials

15.1 Rejection

15.10 Intermediates and APIs failing to meet established specifications should be rejected. Rejected materials should be identified as such and quarantined.

15.11 Rejected materials may be reprocessed or reworked and used, provided there are written procedures in place and the reprocessed or reworked materials meet appropriate specifications.

15.12 The disposition of rejected materials should be recorded.

15.13 When a batch of material is rejected, an evaluation as to whether other batches could have been similarly affected, should be carried out.

15.2 Reprocessing and Reworking

15.20 Due to the potential for formation of by-products, reprocessing of an intermediate or API by repeating a chemical reaction should be preceded by a careful evaluation to ensure that the quality of the final API is not adversely impacted. Where such reprocessing occurs, written process control procedures should be approved by the Quality Control Unit that clearly specify the conditions and limitations of repeating chemical reactions. In addition, the procedures should establish how reprocessing will be evaluated, and what additional tests will be conducted on the reprocessed material to show that the resulting material is of a quality comparable to that normally produced by the process. These tests may include at a minimum, assays for potency, complete impurity profiles, stability testing, and physical attributes testing.

15.21 Reprocessing by physical manipulations (e.g., recrystallisation, dissolution, filtration, milling), if conducted using procedures used to manufacture the original batch, is generally acceptable. However, if such reprocessing is used for a majority of batches,

then the original process is not considered validated, and such reprocessing should be included as part of the standard manufacturing procedure.

15.22 Reprocessing by physical manipulation to improve purity or physical properties of intermediates and APIs would be justified if:

- The reason for non-conformance of the batch or material is evaluated to determine its suitability for reprocessing;
- All reprocessing procedures should be reviewed and approved by the Quality Control Unit. These procedures should clearly specify the conditions and limitations for reprocessing by physical manipulations;
- Either the appropriate copy of the original master batch record my be used or a specific batch production record should be generated to cover the reprocessing step(s) and subsequent handling;
- Appropriate tests should be conducted on the reprocessed material to ensure that reprocessing does not adversely affect the identity, strength, quality, or purity of the intermediate or API. These tests may assay for potency, physical attributes, and impurity profiles. In all cases, the significance of the non-conformance and its impact on the critical quality attributes of the intermediate or API would determine how much analytical data is sufficient to justify the reprocessing;
- Reprocessing operations should be subjected to appropriate evaluation to show that these steps consistently perform the expected functions and result in batches that comply with all established standards, specifications, and characteristics.

15.23 Reworking batches that do not conform to established standards or specifications, by using processing steps that are different from the validated process should entail extensive investigation, evaluation, and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Validation of reworking procedures is critical and should clearly show that reworking does not adversely affect the identity, strength, quality, or purity of the intermediate or API. Procedures should provide for comparing the impurity profile of each reworked batch against batches manufactured by the validated process. Often, the reworked material may necessitate examination by sensitive analytical procedures, such as those used for qualifying reference standards.

15.3 Recovery of Materials and Solvents

15.31 Secondary recovery (from mother liquor or filtrates) of reactants, intermediates, or the API is acceptable, provided that approved procedures exist for the recovery and that the recovered materials meet specifications suitable for their intended use.

15.32 Fresh and recovered solvents and reagents may be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.

15.4 Returns

15.40 Returned APIs should be identified as such and quarantined.

15.41 If the conditions under which returned APIs have been stored or shipped before or during their return, or if the condition of their containers casts doubt on their quality, the returned API should be destroyed unless thorough examination prove that the product meets appropriate specifications.

15.42 Records of returned APIs should be maintained.

16 Complaints and Recalls

16.00 All complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.

16.01 Records of complaints should be retained in order to evaluate trends, product-related frequencies, and severity with a view to taking additional, and if necessary, immediate corrective action.

16.02 There should be a written procedure which defines the circumstances under which a recall of an API should be considered.

16.03 The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated.

16.04 In the event of a serious and potentially life-threatening situation local and national authorities should be informed and their advice sought.

17 Contractors

17.00 Contract manufacturers and laboratories should be evaluated by the contract giver to ensure that CGMP requirements are followed for the specific operations occurring at the contract sites.

17.01 There should be a written and approved contract between the contract giver and the contract acceptor, which defines in detail the responsibilities of each party.

17.02 The contract should permit the contract giver to audit the contract acceptor.

17.03 The contract acceptor should not pass to a third party any of the work entrusted to him under the contract without the contract giver’s prior evaluation and approval of the arrangements.

17.04 Manufacturing and analytical records should be kept by, or readily available to, the contract giver.

17.05 The contract giver is ultimately responsible for the quality of the materials or services delivered.

18 APIs for Clinical Trials

18.1 Quality Assurance Measures

18.10 Appropriate quality control measures and CGMP concepts should be applied in the production of APIs for clinical trials with a suitable mechanism of approval of each batch.

18.11 The manufacturing practices used in the production of clinical API should be consistent with the stage of development. Process and analytical methods should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from pre-clinical stages through Phase III. However, once drug development reaches the stage where a new molecular entity is produced for use in drug products intended for clinical trials in humans or animals, manufacturers should ensure that clinical APIs are manufactured in qualified facilities using appropriate production and control procedures to ensure the safety, quality, and homogeneity of the API.

18.2 Quality Control Unit

18.20 An independent Quality Control Unit similar to that used in commercial production should be established in clinical production of APIs for the approval or rejection of each batch of API

18.21 Some of the testing functions commonly performed by the Quality Control Unit may be performed within other areas.

18.22 Quality control measures should include a system for testing of raw materials, packaging materials, intermediates, and APIs.

18.23 Labelling for APIs intended for clinical trials should be appropriately controlled and identified as for investigational use.

18.3 Equipment and Facilities

18.30 During all phases of clinical development, including the use of small scale facilities or laboratories to manufacture batches of clinical APIs, procedures should be in place to ensure that equipment is calibrated, clean and suitable for its intended use.

18.31 Procedures for the use of facilities should ensure that materials are handled in a manner that avoids the risk of contamination and cross-contamination.

18.4 Control of Raw Materials

18.40. Raw materials used in early stages of clinical API production should be evaluated by testing, or received with a supplier's certificate of analysis and subjected to identity testing.

18.41 The suitability of a raw material from a new supplier may be determined before use based on acceptability in small-scale reactions (i.e., use testing) rather than on analytical testing alone.

18.5 Production and Process Controls

18.50 Laboratory notebooks or batch records may be used to document the production of clinical APIs. These should include all pertinent production materials, equipment, processing, and scientific observations.

18.51 Expected yields may be more variable and less defined than the expected yields used in commercial processes.

18.6 Validation

18.60 At early clinical stages, where a single batch or API may be produced and where significant processing changes may make batch replication difficult or inexact, only limited process validation may be possible.

18.61 In situations where a single or limited number of API batches are produced for clinical trials, data from extensive in-process and end product testing may be used to demonstrate that the process yields an API meeting established specifications and quality characteristics. More comprehensive process validation should be conducted as additional batches are produced under replicated conditions.

18.62 If manufacturing of APIs at a pilot scale or small scale continues for an indefinite period, these production processes should be validated.

18.63 Once pilot or small scale production processes are scaled up, the commercial production process should be subjected to full validation studies.

18.7. Change Documentation

18.70 Changes to the process are expected during clinical development as knowledge of the process is gained and the production is scaled up.

18.71 All process modifications should be adequately documented.

18.8 Laboratory Controls

18.80 All analyses performed to evaluate a batch of API for clinical trials should be scientifically sound.

18.81 A system for retaining reserve samples should be used. This system should ensure that reserve samples are retained for an appropriate length of time after approval, termination, or discontinuation of an appication. Additional reserve samples should be maintained for API batches used in pivotal toxicological and/or biobatches.

18.9 Documentation

18.90 A system should be in place to ensure that information gained during the development and the production of APIs for clinical trials is documented. This information should be integrated into the process development report.

18.91 The development and implementation of the analytical methods used to support the release of a batch of API for clinical trials should be appropriately documented.

18.92 All modifications should be adequately documented.

18.93 A system for retaining production and control records should be used. This system should ensure that records are retained for an appropriate length of time after the approval, termination, or discontinuation of an application.

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